Translation

PCT/JP2003/003623

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 03-F-014PCTA	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP2003/003623	International filing date (*day/month/year*) 25 March 2003 (25.03.2003)	Priority date (*day/month/year*) 25 March 2002 (25.03.2002)

International Patent Classification (IPC) or national classification and IPC
C12N 5/08, 15/09, A01K 67/027, C12P 21/08, C07K 16/18, C12N 5/18, A61L 27/00

Applicant
JAPAN SCIENCE AND TECHNOLOGY AGENCY

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 August 2003 (25.08.2003)	03 March 2004 (03.03.2004)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/003623

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-37, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 2-9, 11-20, 23-29, 31-33, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1, 10, 21, 30, filed with the letter of 25 February 2004 (25.02.2004)

☒ the drawings:

pages 1-2, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:

pages 1-2, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☒ the claims, Nos. 22
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP03/03623

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

As described in documents 1 and 2 listed below, making a differentiation and proliferation of human hepatic stem cells (human hepatic progenitor cells) to provide such cells was publicly known prior to the priority date, and so cannot be a special technical feature in accordance with PCT Rule 13.2.

Accordingly, the subject matters of claims 30-32 that relate to monoclonal antibodies that recognize human hepatic stem cells specifically are not so linked with the subject matters of the other claims that relate to methods for proliferating human hepatocytes by using immuno-deficient mice with hepatopathy as to form a single general inventive concept. The claims of the present application therefore describe the following two inventions.

(1) Invention described in claims 1-29 and 33 that relates to proliferating human hepatocytes by using immuno-deficient mice with hepatopathy
(2) Invention described in claims 30-32 that relate to monoclonal antibodies that recognize human hepatocytes specifically, and hybridomas that produce the said antibodies

Document 1: WO, 00-03001, A1 (Rhode Island Hospital), 20 January, 2000 (20.01.00)
Document 2: WO, 00-43498, A1 (Univ. of North Carolina), 27 July, 2000 (27.07.00)

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____ .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-21, 23-26, 33	YES
	Claims	27-32	NO
Inventive step (IS)	Claims		YES
	Claims	1-21, 23-33	NO
Industrial applicability (IA)	Claims	1-21, 23-33	YES
	Claims		NO

2. Citations and explanations

Document 1: WO, 01-87059, A1 (Japan Science and Technology Corp.), 22 November, 2001 (22.11.01), and JP, 2002-45087, A
Document 2: WO, 00-03001, A1 (Rhode Island Hospital), 20 January, 2000 (20.01.00), & EP, 1097193, A1, & US, 6129911, A, & JP, 2002-520015, A
Document 3: WO, 00-43498, A1 (Univ. of North Carolina), 27 July, 2000 (27.07.00), & EP, 1147179, A2, & US, 2002-0182188, A1, & JP, 2002-534974, A
Document 4: JP, 61-189299, A (Nisshin Four Milling Co.), 22 August, 1986 (22.08.86)
Document 5: EP, 682106, A2 (Research Development Corp. of Japan), 7 May, 1996 (07.05.96), & US, 6004810, A, & JP, 8-112092, A
Document 6: Int. Immunol., 2000, Vol. 12, No. 4, pages 555-562
Document 7: EP, 990663, A2 (Sankyo Co., Ltd.), 5 April, 2000 (05.04.00), and JP, 2000-166574, A

Claims 1-5, 7-14, 16-18, 21-24, 27-29 and 33

The subject matters of claims 1-5, 7-14, 16-18, 21-24, 27-29 and 33 do not appear to involve an inventive step in view of document 1 cited in the ISR.

Document 1 describes immuno-deficient mice with hepatopathy in which human hepatocytes are transplanted and substantially bear the hepatic function of those mice as recipients, and describes, particularly, that it is possible to transplant small hepatocytes able to actively proliferate *in vivo* into such mice, and have them proliferate rapidly and form a group of cells able to perform the hepatic function in the bodies of the recipients for a short time. It also describes there that the said immuno-deficient mice are created by administering an immunity suppressor and that such mice are used to evaluate the toxicity to hepatic cells of a tested substance by administering that substance.

It is well known to a person skilled in the art that there occurs a rejection (immunoreaction) in a mouse when human hepatocytes that are foreign organisms to the mouse are transplanted into the body of the mouse, and so a person skilled in the art would generally administer an immunity-suppressing agent not only before but also after the transplantation. It would be an obvious effect for a person skilled in the art that administering an immunity-suppressing agent to such mice suppresses their rejection (immunoreaction), which increases their survival rate and promotes the proliferation of human hepatocytes.

Even without recognizing that the mortality of such mice rises because of attacks by human complements produced by human hepatic cells, it is a general practice to administer them an immunity-suppressing agent after the transplantation, and so such secondary effect is not taken into consideration for the invention concerned.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of : V

Claims 6 and 15

The subject matters of claims 6 and 15 do not appear to involve an inventive step in view of documents 1, 6 and 7 cited in the ISR.

Documents 6 and 7 describe that anti-Fas antibodies have an apoptosis-inducing activity for hepatocytes. According to document 1, u-PA would only be expressed in hepatocytes so that the hepatocytes of the recipient could be damaged, but it is considered to be obvious for a person skilled in the art that hepatocytes of the recipient are damaged by means of an anti-Fas antibody instead of u-PA expressed.

Claims 27-32

The subject matters of claims 27-32 do not appear to be novel or to involve an inventive step in view of documents 2 and 3 cited in the ISR.

Documents 2 and 3 describe that matured hepatocytes or a hepatic aid device (artificial liver) are obtained by the proliferation and differentiation of human hepatic stem cells (hepatic progenitor cells). The antibody of document 2 that bonds specifically to CCAM present in matured hepatocytes, and the anti-ICAM antibody, anti-CD34 antibody, anti-CD38 antibody, etc., of document 3 that bond specifically to matured hepatocytes are indistinguishable from the antibodies described in claims 30 and 31.

It is considered to be obvious for a person skilled in the art to select among the antibodies described in documents 2 and 3 those that recognize human hepatocytes specifically.

Claims 19, 20, 25 and 26

The subject matters of claims 19, 20, 25 and 26 do not appear to involve an inventive step in view of documents 1-3 cited in the ISR.

It is considered to be obvious for a person skilled in the art to isolate a group of hepatocytes that are allowed to proliferate and differentiate in the recipient, described in document 1, by means of the antibodies that bond specifically to matured hepatocytes, described in documents 2 and 3.

Claims 30-32

The subject matters of claims 30-32 do not appear to be novel or to involve an inventive step in view of document 4 cited in the ISR.

Document 4 describes monoclonal antibodies that bond specifically to human hepatocytes antigen, and hybridomas that produce the said antibodies.

It is considered to be obvious for a person skilled in the art to select among the antibodies described in document 4 those that recognize human hepatocytes specifically.

Claims 27-29

The subject matters of claims 27-29 do not appear to be novel or to involve an inventive step in view of document 5 cited in the ISR.

Document 5 describes hepatic parenchyma cells that have an ability of cloning proliferation, and a method of subculture of such cells. The human hepatocytes described in claim 27 are indistinguishable from the hepatic parenchyma cells described in document 5.